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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,157	04/16/2004	Susan L. Lindquist	17481-003001	8571

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/826,157	LINDQUIST ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,7-17,22,23 and 27* is/are pending in the application.

4a) Of the above claim(s) *23 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 1/26/09. Claims 1, 7-17, 22, 23 and 27 are pending in the application. Claims 23 and 27 are withdrawn and therefore, claims 1, 7-17 and 22 are under examination.

Claims 23 and 27 are commensurate in scope with the allowed products. However, until an elected product claim is found allowable, an otherwise proper restriction between product claims and process claims may be maintained. At such a time that an allowable claim is identified, claims 23 and 27 will be examined to ensure that they also meet all criteria for patentability including the requirements of 35 USC 101, 101, 103 and 112.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a yeast cell comprising two integrated copies of an expression construct comprising a nucleic acid encoding a protein comprising wild-type alpha synuclein or mutant A53T under control of a promoter wherein the protein is toxic to the cell such that the cell is non-viable, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope

with these claims. **This rejection is maintained for reasons of record in the action mailed 1/26/09.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The specification teaches that alpha synuclein is associated with protein misfolding disease or condition such as neurological disorder or neurodegenerative conditions in humans. To this end, the specification teaches specifically that there are only two α-synuclein peptides, wild-type (WT) and mutant A53T (see e.g. page 44, line 5-8) that are toxic to yeast cells in ways that can be used to identify drugs which inhibit misfolding and/or abnormal processing of proteins and thus can be used in prevention or treatment. Specifically, the specification teaches that that yeast cells expressing these proteins "recapitulate hallmarks of abnormally processed protein biology such as 1) membrane association; 2) formation of inclusions; 3) differences in the behavior of wild type and A53T versus A30P; 4) ubiquitination; 5) toxicity; 6) interactions with mutant huntingtin (htt); 7) oxidative stress; and 8) inhibition of PLD". Hence, applicants proposed development of yeast cells comprising nucleic acid expressing toxic levels of alpha-synuclein for purposes of establishing cells exhibiting the toxic effects of alpha-synuclein (AS) to assay and analyze the toxicity of AS and methods of inhibiting these. Applicants have

demonstrated in post-filing publications that two copies of a-synuclein are required to affect growth and cell viability (see e.g. Cooper et al, 2006, page 324, col 2 and Outeira and Lindquist, 2003, page 1773).

The instant claims have been assessed and found to have a level of unpredictability for the following reasons. First, it is not clear how levels of protein are altered to attain the recited goals 1) wherein the protein is toxic to the cell 2) wherein expression of the nucleic acid renders the cells non-viable 3) wherein expression of the nucleic acid arrests growth of the cell and 4) wherein the cell expresses a toxicity inducing amount of the proteins. The specification simply teaches integration of two expression constructs wherein expression is under control of an inducible promoter and wherein expression results in loss of viability, Hence, it is not clear what distinguishes the ability of these peptides to mediate toxicity versus non-viability versus cell growth arrest. In fact, the only experimental procedures provided by applicants are use of cells wherein the expression vector is integrated into the yeast genome and A53T or WT synuclein is under control of an inducible promoter as demonstrated in figure 3 where expression results in cell death. As to construction of cells, the specification teaches, "To express alpha synuclein proteins in yeast cells, a variety of expression constructs that permitted different levels of expression and different patterns of regulation of aS proteins were generated. For example, 2.mu. vectors are present in high copy and permit high levels of expression, but they have the disadvantage of varying in number from cell to cell and instability. Integrating constructs are extremely stable but produce lower levels of expression. Constitutive promoters allow expression in normal media, but inducible promoters allow to control the levels and timing of expression. Controllable expression is of particular interest when dealing with potentially toxic proteins, to

enhance transformation efficiencies and avoid the accumulation of mutations in the genome that alter aS function and toxicity. Western blotting of aS, A53T, and A30P demonstrated similar levels of accumulation." Hence, it appears that the cells comprising integrated copies of expression vectors require the nucleic acid under control of a promoter. Given the lack of guidance in the specification, the large and diverse group of peptides recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention.

Response to Argument

Applicants' arguments filed 1/26/09 have been fully considered but they are not persuasive. The functionality of the invention is based upon expression of alpha synuclein. Absent a promoter, it is not clear how the protein is expressed.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 7-15, 17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Lindquist et al (US 7,045,290; see entire document) as evidenced by Sherman (Nine Yeast Vectors downloaded 7/18/08). **This rejection is maintained for reasons of record in the office action mailed 3/26/08 and 7/24/08 and restated below.** The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C.

102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Lindquist et al teach that expression of WT and mutant A53T is toxic to cells (see e.g. legend to figure 3). Lindquist teaches expression of WT and A52T in yeast cells via an integrative vector i.e. pRS304 and pRS306 for expression of alpha-synuclein (AS) as recited in claims 1, 9, 10, 17 and 18 as well as mutant and human AS as recited in claims 5, 6, 20 and 21 (see e.g. col 4, line 62- col 5, line 3). The AS may be a fusion peptide linked to a fluorescent peptide such as GFP as recited in claims 11-13. The yeast may be for example *Saccharomyces* as recited in claim 7 and 22 such as yeast cells comprising a mutation in pdr3 as recited in claims 14 and 15 (see e.g. col 10, line 28-49). As demonstrated in figure 3, the cells are non-viable (see growth characteristics in row 1 versus 2 for example. Vectors are described which allow integration of two copies or more as recited (see e.g. col 21) and as well comprise inducible promoters such as GPD (see e.g. col 23, line 38-60) as recited in claim 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquist et al (US 7,045,290; see entire document) as applied to claims 1, 7-15, 17 and 22 above, and further in

view of Frate (US 2004/0115792; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/26/08 and 7/24/08 and restated below.**

Applicants claim a yeast cell comprising a disrupted PDR5 gene for expression of a toxic amount of a-synuclein.

The teachings of Lindquist et al are described above and are applied as before except; Lindquist et al do not teach use of a cell comprising a disruption in PDR5.

Frate teaches use of a yeast cell line comprising a disruption of PDR5 for testing genotoxicity and cytotoxicty of environmental contaminants. Frate chose use of this cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic compounds can be analyzed in the context of the cell (see e.g. ¶ 0066-0067).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cells comprising a deletion in pdr3 as taught by Lindquist et al with the cells comprising a pdr5 deletion as taught by Frate because Lindquist et al teach that it is within the skill of the art to assess toxicity of substances in a yeast cell expressing alpha-synuclein and because Frate teaches that it is within the ordinary skill of the art to use a pdr5 deficient cell as a host cell for analysis of toxic compounds. One would have been motivated to do so in order to receive the expected benefit of unhampered comparison of cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic compounds can be analyzed in the context of the cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments filed 9/26/07 have been fully considered but they are not persuasive. Applicants argue that column 21 does not describe construction of yeast cells that contain two integrated copies of an expression construct encoding alpha-synuclein. The Lindquist reference can only be considered as a whole and while col 21 does not set forth all of the details of a yeast cell comprising two integrated copies of alpha-synuclein, the totality of the teachings allow one to construct such a cell. Specifically, Lindquist teaches expression of WT and A52T in yeast cells via an integrative vector i.e. pRS304 and pRS306. These vectors are specifically utilized vectors in the instant invention and one would expect that the functions of these vectors provided to the instant invention would be the same as those resulting from their use in preparing the cell of Lindquist et al. In other words, their introduction into the yeast cell would inherently result in integration as they are integrative vectors. And as they are relied upon in the instant invention to create two integrated copies, this function should be an inherent result of their use. Specifically, Lindquist et al teach, "In some embodiments of the invention a yeast cell expresses a polypeptide that includes all or part of an alpha synuclein polypeptide" and "In some embodiments of the invention, the alpha synuclein polypeptide is wild-type (SEQ ID NO:2), while in other embodiments it is mutated. The mutation may be a deletion, insertion, or substitution in the polypeptide. In specific aspects of the invention, the alpha synuclein polypeptide comprises a A53T mutation, which is a substitution of threonine for alanine at position 53. In other aspects the alpha synuclein polypeptide comprises a A30P mutation, which is a substitution of proline for alanine at position 53.b (see col 4, line 49-col 5, line 3). As well, in column 44, example 9, "Wild-type (WT), A53T and A30P alpha -synuclein cDNAs were a

kind gift from Dr. Peter Lansbury. WT, A53T, and A30P sequences were subcloned into p426GPD, p416GPD, p423GPD and p425GPD (Mumberg et al., 1995) by standard molecular biology procedures. GFP, CFP and YFP fusions which are fusions of alpha -synuclein in frame with GFP, CFP or YFP were constructed by inserting the XFP (X meaning G, C or Y) coding sequence in frame with alpha -synuclein in the same vectors. The XFP fusions were also subcloned into pRS306 and pRS304 under the regulation of a GAL1-10 promoter and with a Cyc1 terminator region." This last passage teaches construction of a vector comprising aS coding sequences in an integrative vector that should absent evidence to the contrary integrate at least two copies into a cell.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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